

MINI-REVIEW

Molecular bases of growth hormone deficiency

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INTRODUCTION

Short stature is a common pediatric problem that requires a precise clinical study to decide between a normal variation or an underlying disease. In a normal population of children, only 20% of cases with two standard deviations (SD) below the mean for height are considered as having pathologic short stature. Children representing the other 80% have been classically considered as presenting familial short stature or constitutional growth delay. On the other hand, the majority of children three SD below the mean for height have pathologic short stature (Mahoney, 1987).

In order to evaluate a pathologic short stature physical measurements must be performed to determine a proportionate or disproportionate body structure. Further characteristics must also be evaluated in order to better understand the origin of this pathology.

Although growth retardation represents a complex feature for study, some causes have been extensively analyzed, particularly the growth hormone deficiency, which afflicts only a small fraction of children affected with short stature.

CLINICAL AND GENETIC FEATURES OF GROWTH HORMONE DEFICIENCY

Growth hormone deficiency has been defined in short stature patients which show low levels or non-measurable circulating growth hormone (GH) after different stimulation tests for GH synthesis and secretion. Six different types of growth hormone deficiency have been described according to the hormone production

and the pattern of inheritance (Phillips, 1983) (Table I). Although these may involve hypothalamic or hypophysial factors, such as hormones, receptors, signal transduction regulators and transcription factors, only in few cases the gene and the molecular defect have been identified.

Table I describes the different types of growth hormone deficiency. Four of them have been defined as "Isolated Growth Hormone Deficiencies" (IGHD), indicating that the only endocrine abnormality involves the GH. The last two deficiencies are defined as panhypopituitary dwarfism, in which patients show other endocrine failures such as the thyroid stimulating hormone (TSH) and prolactin, in addition to low GH levels.

IGHD type IA: This defect, which is autosomal recessive, is the most severe form of IGHD. Affected patients present a short body length at birth, develop severe dwarfism by six months of age, and show an early growth retardation resulting in extreme dwarfism in adulthood (Phillips *et al.*, 1986). Some of these children are refractory to exogenous GH treatment.

IGHD type IB: These patients are characterized by low but detectable levels of GH. This deficiency has also an autosomal recessive mode of inheritance.

IGHD type II: This type has an autosomal dominant inheritance. The GH levels are low but detectable and the clinical severity varies between kindred (Phillips *et al.*, 1986).

IGHD type III: This deficiency is X-linked and also shows a diminished GH level.

ENDOCRINE REGULATION OF GH

In order to better comprehend the molecular causes of this pathology we must review the GH gene structure, the expression and secretion regulation of GH, and the GH function at the endocrine level.

Table I - Nosology of growth disorders associated with growth hormone deficiency.

Disorder	Mode of inheritance	Endocrine defect
IGHD		
IA	Autosomal recessive	GH absent
IB	Autosomal recessive	GH decreased
II	Autosomal dominant	GH decreased
III	X-linked	GH decreased
Panhypopituitary dwarfism		
IA	Autosomal recessive	GH, TSH, prolactin decreased
IB	Autosomal dominant	GH, TSH, prolactin decreased

IGHD, Isolated growth hormone deficiencies; GH, growth hormone; TSH, thyroid stimulating hormone.

Growth is regulated in humans by a complex cascade of hormones (Figure 1), including the neuro-endocrine peptides GH-releasing hormone (GHRH) and somatostatin, the pituitary protein GH, and the insulin-like growth factor 1 (IGF-I). The actions of these hormones are mediated by specific cell-surface receptors, all of which have been identified and cloned

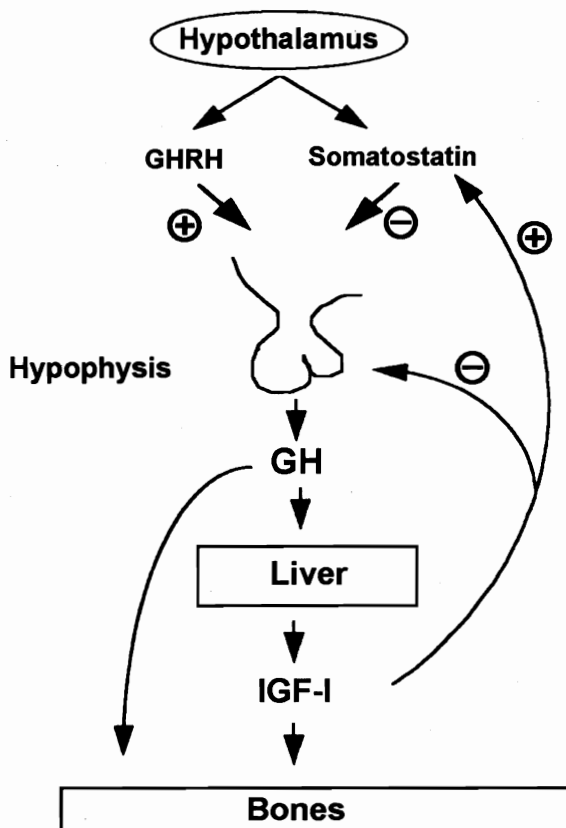


Figure 1 - Schematic representation of human GH regulation. GH: Growth hormone; IGF-I: insulin-like growth factor 1; GHRH: growth hormone releasing hormone. (+) and (-) Indicate stimulation and repression of a pathway.

(Ullrich *et al.*, 1986; Leung *et al.*, 1987; Yamada *et al.*, 1992; Mayo, 1992).

The two hypothalamic factors, GHRH and somatostatin, regulate GH expression and secretion. GHRH is secreted by the hypothalamus as a 44-amino acid peptide (Gelato and Merriam, 1986). It activates a specific G-protein-coupled receptor present in the somatotrophs (Velicelebi *et al.*, 1986), increasing intracellular cAMP and activating a signal transduction pathway which finally activates GH expression and secretion (Bilezikjian and Vale, 1983; Labrie *et al.*, 1983). Somatostatin is a tetradecapeptide which inhibits GHRH-activated adenylate cyclase leading to a decrease in cAMP levels and inhibiting GH release. The inhibitory effect of somatostatin seems to be exerted through a Gi protein, coupled to a specific receptor having the characteristic 7 transmembrane domains (Yamada *et al.*, 1992).

The growth hormone is secreted by the anterior pituitary as a 22-kDa protein. It circulates in plasma complexed to specific proteins called GH binding proteins (GHBP). GH finally binds to a specific cell surface receptor in the liver. The GH receptor is a member of the cytokine receptor family (Kelly *et al.*, 1991). GH binding causes dimerization of the receptor, activation of JAK2 tyrosine kinase, activating a variety of signaling molecules, including MAP kinases, phosphatidylinositol 3' kinase, protein kinase C and Stat transcription factors (Carter-Su *et al.*, 1996). The most important gene expression stimulated by GH in the liver is IGF-I (Mathews *et al.*, 1986; Bichell *et al.*, 1992).

Circulating IGF-I is bound to six specific proteins named IGF binding proteins (IGF-BP, 1-6) being IGF-BP3 the most abundant (Casanueva, 1992). IGF-I stimulates epiphyseal cartilage width and longitudinal bone growth promoting growth plate chondrocytes (Trippel *et al.*, 1989).

Recently, a synthetic hexapeptide, the growth hormone-releasing peptide (GHRP), derived from enkephalins has been described to be a potent stimulator of pituitary GH release (Bowers *et al.*, 1993). Administration of this peptide to growth hormone deficient patients produces a significant GH response in a high fraction of these children (Mericq *et al.*, 1995). A specific receptor that binds to GHRP has been cloned from a human cDNA pituitary library, supporting the notion that GHRP mimics a yet undiscovered hormone (Howard *et al.*, 1996).

Thyroid hormones also play a special and relevant role in the regulation of somatic growth and GH secretion. These hormones exert their effects by acting directly at the pituitary level as well as in the hypothalamus (Nyborg *et al.*, 1984). Hypothyroidism in

humans is associated with low GH basal levels and reduced GHRH-stimulated GH secretion (Williams *et al.*, 1985).

It has also been shown that glucocorticoids are important regulators of GH secretion in humans (Thakore and Dinan, 1994), exerting their action at different levels, such as the somatostatin action, the expression of the GHRH and GH receptors, and GH expression itself (Dieguez *et al.*, 1996; Miller and Mayo, 1997; Nogami *et al.*, 1997).

THE GROWTH HORMONE LOCUS AND ITS REGULATION

The growth hormone locus is localized in a region mapped to chromosome 17q23-24 spanning 65,000 bp (Xu *et al.*, 1988). This locus was completely sequenced by Chen *et al.* in 1989 and contains five different genes, named hGH-N, hCS-L, hCS-A, hGH-V and hCS-B, which share more than 90% homology and are separated by intergenic regions of 6 to 13 kb. The analysis of gene expression by screening of pituitary and placental cDNA libraries showed that hGH-N is only transcribed in somatotrophs of the anterior pituitary whereas the other four genes are expressed only in placental tissues (Chen *et al.*, 1989). The differential gene expression of the five genes is controlled by different transcriptional factors which bind to enhancers and silencer elements.

The hGH-N gene is dependent on promoter-proximal elements that include two binding sites for the transcriptional factor Pit-1 (Ingraham *et al.*, 1988; Nelson *et al.*, 1988) and an Sp1 site (Lemaigre *et al.*, 1990). Also a putative GRE (glucocorticoid responsive element) binding site is found 100 bp upstream of the distal Pit-1 site (Lefevre *et al.*, 1987). Besides these promoter-proximal regulatory sequences, a set of other regulatory elements far upstream have been described for the GH gene which seem to be involved in tissue specific expression of pituitary and placental genes (Jones *et al.*, 1995).

The four placental expressed genes have Pit-1 binding sites at their 5' promoter proximal sequences (Lemaigre *et al.*, 1989), and it has been demonstrated that Pit-1 mRNA is present in human placental tissues (Bamberger *et al.*, 1995). These results indicate that transcription of the four placental genes is also under Pit-1 control. It is difficult to reconcile the fact that the differential expression occurs, since Pit-1 is regulating all of the genes in the GH locus. However, other regulatory elements such as pituitary-specific repressor sequences located 2 kb 5' to each gene, and placenta-

specific enhancer sequences located 3' of the hCS genes have been shown to be involved in the tissue specific expression (Walker *et al.*, 1990; Nachtigal *et al.*, 1993).

GH GENE DEFECTS ASSOCIATED TO IGHD

IGHD IA

In 1981, Phillips *et al.* first described a Swiss family with growth hormone deficiency resulting from a deletion of 7.5 kb including the hGH-N gene. Subsequent studies have shown hGH-N deletions in children from different ethnic origins. Among these studies three different deletion sizes of 7.6 kb, 7.0 kb and 6.7 kb have been described (Nishi *et al.*, 1984; Rivarola *et al.*, 1984; Braga *et al.*, 1986; He *et al.*, 1990; Kamijo and Phillips, 1992; Mullis *et al.*, 1992; Aguirre *et al.*, 1993). The most frequent deletion size is 6.7 kb, and the less frequent is 7.0 kb which has been found in one Chinese family (He *et al.*, 1990) and in four Chilean families (Aguirre *et al.*, 1993, and Carvallo, P., unpublished results). Initially the analysis of IGHD IA was performed through Southern blots (Phillips *et al.*, 1981), but Vnencak-Jones *et al.* (1990) described a much simpler analysis by PCR amplification, followed by restriction digestion. In general the frequency for the occurrence of this type of deletions is very low, being close to 10% of IGHD patients.

Heterozygous GH gene deletions, frameshift and nonsense mutations have also been described in IGHD IA patients (Phillips and Cogan, 1994). These frameshift and nonsense mutations affect the GH signal peptide (Figure 2, exon II) leading to a truncated peptide and preventing any mature GH protein.

IGHD IB

In these patients no deletions of the hGH-N gene are present but occasional point mutations have been found. One such mutation involves a G-T and a G-C change in the first base of the 5' donor splice of intron IV (Figure 2, IVS 4). This mutation activates a cryptic splice site 73 bases upstream of the exon IV donor splice site, leading to a loss of amino acids 103-126, and creating a frameshift that alters the amino acid sequence of exon V (Phillips and Cogan, 1994). Another mutation described is a deletion of 2 bp in exon III resulting in a frameshift within this exon and causing a premature stop codon (Phillips and Cogan, 1994). However, these mutations have been described in only

one family each. In this regard other genes such as the GHRH and its receptor have been studied in different patients. In our experience (Carvalho, P., unpublished results) and in other reports, no mutations in these genes have been found in a representative number of patients (Perez Jurado *et al.*, 1994; Cao *et al.*, 1995). Wajnrajch *et al.* (1996) are alone in reporting a mutation localized in the extra-cellular domain of the GHRH receptor in IGHD IB patients. This mutation is a G-T transversion that results in the creation of a stop codon at position 265, leading to a truncated receptor lacking any of the transmembrane domains.

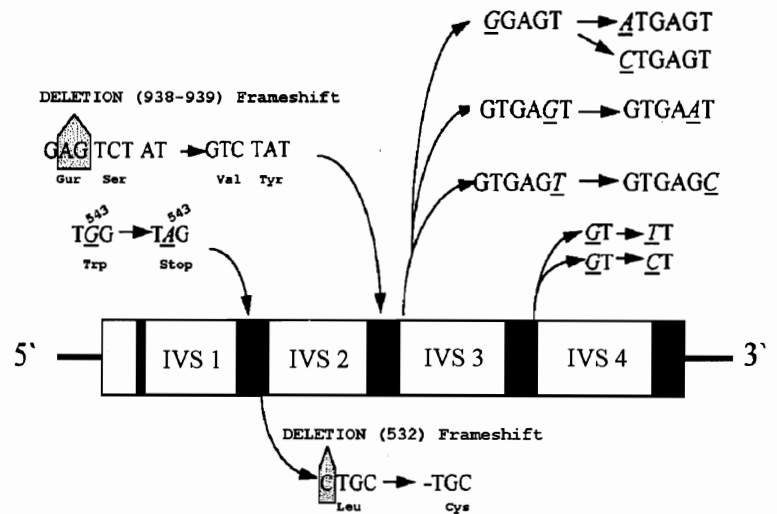


Figure 2 - Schematic representation of the GH gene. Exons are shown in black and introns are indicated as IVS 1 to 4. Point mutations are indicated in italics and underlined. Deletions are in boxes.

IGHD II

All mutations described until now in this category involve the 5' donor splice site of intron III (Figure 2, IVS 3). Four different point mutations (Figure 2, IVS 3) have been described: a G-A transition and a G-C transversion in the first base of intron III, a G-A transition in the fifth base, and a T-C transition in the sixth base (Cogan *et al.*, 1994, 1995; Binder and Ranke, 1995; Missarelli *et al.*, in press). All these mutations affect the normal splicing of the GH premRNA leading to a deletion of exon III and the skipping of amino acids 32-71, as demonstrated by transfection experiments of the mutated genes (Binder and Ranke, 1995; Missarelli *et al.*, in press).

The exon excluded during the altered splicing contains amino acids 32 to 71 of GH. The structure of the GH hormone consists of a four-helical bundle. Residues 35 to 71 of helix 1 form a crossover connection with helix 2 and, in addition, Cys⁵³ of helix 1 links to Cys¹⁸⁹ in helix 4 (De Vos *et al.*, 1992). Therefore, the loss of amino acids 32 to 71 eliminates helix 1 with Cys⁵³, thus altering an important feature in the GH structure. How this GH structure becomes a dominant negative form is not yet known, however it has been proposed that the deletion of Cys⁵³ leaves one of the three remaining cysteines unpaired and available for intermolecular bond formation with another GH molecule. Therefore, the dominant negative effect could occur through inhibition of GH secretion from secretory granules of pituitary cells (Cogan *et al.*, 1994).

It is interesting to note that until now four different mutations in intron III are responsible for IGHD type II, causing a dominant negative form of the growth hormone. Further studies are required in order to evaluate the dominant negative feature of this mutation.

IGHD III

Until now there is no precise information which defines the gene(s) involved in this X-linked trait for IGHD. Some affected individuals present agammaglobulinemia associated with IGHD (Conley *et al.*, 1991; Duriez *et al.*, 1994). This finding suggests that a contiguous gene deletion disorder of Xq21.3-q22 may occur in these cases. Interestingly, other patients with IGHD show a deletion of Xq22.3 or a duplication of Xq13.3-q21.2, suggesting that multiple loci may cause IGHD III (Ogata *et al.*, 1992; Yokoyama *et al.*, 1992).

CONCLUSIONS

The molecular bases of isolated growth hormone deficiency seem to be very variable. Although some mutations have been described in the GH gene and the GHRH receptor gene, a considerable fraction of IGHD children remain without a molecular diagnosis.

In relation to the genetic causes of growth failure which involves other clinical and endocrine features, besides IGHD, different molecular defects have been described. Some of these gene defects involve the Pit-I transcription factor, the GH receptor gene, and the IGF-I gene.

Since GH synthesis, secretion and action involve many different hormones and effectors, it is suggestive that other gene defects may be involved in GH deficiency and genetic short stature, besides IGHD.

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